Rate-Dependent AV Delay Optimization in Cardiac Resynchronization Therapy

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Background: *During cardiac resynchronization therapy (CRT), cardiac performance is dependent on an optimized atrioventricular delay (AVD). However, the optimal AVD at different heart rates has not been defined yet during CRT.*

Method: *The effects of an increase in heart rate by pacing or physical exercise on optimal AVD were studied in 36 patients with biventricular pacemakers/defibrillators. The velocity time integral (VTI) in the left ventricular outflow tract (LVOT) was measured with pulsed Doppler either at three different paced heart rates in the supine position or in seated position before and after physical exercise.*

Results: *The baseline AVD was optimized to 99 ± 19 ms in the supine and 84 ± 22 ms in the seated position. When the heart rate was increased by DDD pacing, there was a positive linear relationship between an increase in heart rate, in AVD and in VTI (LVOT-VTI + 0.047 cm/s per 10 beats per minute (bpm) heart rate increase per 20 ms increase in AVD, P = 0.007). A similar but more pronounced relationship was found after physical exercise in the seated position (LVOT-VTI + 0.146 cm/s per 10 bpm heart rate increase per 20 ms increase of AVD, P = 0.013). This effect was observed in patients with and without AV block and mitral regurgitation.*

Conclusions: *In conclusion, the systolic performance of the dilated ventricle, which depends on an elevated preload, is critically affected by the appropriate timing of the AVD during exercise. In contrast to normal pacemaker patients, in CRT the relatively short baseline AVD should be prolonged at increased heart rates. Further studies with other means of measuring exercise cardiac performance are needed to confirm these unexpected findings. (PACE 2005; 28:279–284)*

cardiac resynchronization therapy, exercise, AV delay, congestive heart failure

Introduction

During cardiac resynchronization therapy (CRT), a short atrioventricular delay (AVD), usually in the range of 100–120 ms, is typically used to preexcite the left ventricle and increase preload by coupling atrial contraction to the beginning of ventricular systole.[1–6] However, it is unclear whether AVD should be further shortened, kept constant, or prolonged as heart rate increases. This is an important issue because the failing heart, having a decreased contractile reserve, increases heart rate as the main response to an increase in metabolic demand.[7] Therefore, the purpose of this study was to determine the optimal AVD at various heart rates during CRT. Because of unexpected initial findings in the DDD paced group, we added a second group of patients with a physiologic raise of heart rate after physical exercise.

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Methods

This study was undertaken in 36 patients in sinus rhythm with a biventricular pacemaker/defibrillator (Table I). Optimization of AVD was performed as part of an IRB-approved clinical protocol the day after implantation in 14 patients and in 22 patients during follow up. A set of 8–10 AVDs ranging from 60 ms up to the intrinsic AV interval in steps of 20 ms was programmed in a random order in each patient. To eliminate the effect of different degrees of underlying conduction system disease, only values during biventricular pacing (BVP) were analyzed. In 22 patients, the optimal AVD was determined in the supine position while the heart rate was raised from baseline DDD pacing to the programmed upper tracking rate of the device ranging from 110 to 120/min. Three heart rates at 20 beats per minute (bpm) difference were tested in each patient.

Because the results pointed to an unexpected direction, we studied the second group of 14 patients with intact function of the sinus and atrioventricular node and provoked a physiologic rise of intrinsic heart rate for at least 20 bpm with physical exercise on a treadmill. All the pacemakers

Table I.

Clinical and Baseline Echocardiographic Parameters

	Supine, Pacing (n = 22)	Sitting, Exercise (n = 14)	P value
Age (years)	62.6 ± 8.5	57.9 ± 9.5	0.1
Gender (M/F)	15/7	7/7	
Ischemic cardiomyopathy	19 (86%)	6 (43%)	<0.01
Days after implant	174 ± 154	64 ± 121	0.02
AV block	3		0.2
Mitral regurgitation			
Absent	14	7	
Mild	1	0	
Moderate	5	2	
Severe	2	5	
Ejection fraction	0.17 ± 0.05 (range 0.1–0.3)	0.21 ± 0.08 (range 0.15–0.3)	0.1
Intrinsic QRS duration (ms)	162 ± 26	165 ± 24	0.8
Intrinsic heart rate (bpm)	72 ± 13	74 ± 14	0.5
Optimal AV delay at rest (ms)	99 ± 19	84 ± 22	0.052
Range (ms)	80–160	60–120	

were in atrial sensed mode (VDD or DDD 50) and the sensor was turned off, thereby eliminating the effects of atrial pacing on effective AVD. The optimal AVD was determined in the seated position, before and immediately after treadmill exercise. To account for the variation in heart rate during recovery, echo images were stored with the corresponding cardiac cycle length, which was used for statistical analysis.

Echocardiographic Assessment

Echocardiograms and Doppler evaluation were performed with a standard, commercially available ultrasound system (Sequoia, Acuson/Siemens, Mountain View, CA). For each patient, echo acquisitions were taken in the same body position, either supine or seated. Care was taken to maintain the same transducer position and place the sample volume in the same position in the left ventricular outflow tract (LVOT) within 1 cm below the aortic valve during an entire series of AVD reprogramming. Because changes in left ventricular performance are visible on a beat-to-beat basis in echocardiography, AVDs were reprogrammed as soon as the spectral profiles had been saved, using the same transducer position. At each AVD, pulsed wave Doppler of the LVOT was digitally acquired. Measurements were performed *post hoc* by tracing the Doppler spectral profiles. Ectopic beats and the first postectopic beats were excluded from the analysis. The average of three consecutive beats was employed in the statistical analysis. Only values obtained during ventricular pacing were included in the analysis. Optimal AVD was defined as the AVD that resulted in the maximum LVOT-VTI as described previously.[3] Because the LVOT-VTI was recorded instantaneously from the same transducer position and at the same location, it was considered as an accurate indicator of *relative* changes in forward flow. Echocardiographic data were reviewed by a second investigator blinded to the pacemaker programming.

Statistics

Continuous variables are expressed as mean ± standard deviation and were compared with Student's *t*-test. The effects of AVD and heart rate on velocity time integral (VTI) were determined with mixed linear models for repeated measures. Data were processed using commercially available software (SPSS 9.0 for Windows and SAS 8.1).

Results

Optimization of AVD using LVOT-VTI was feasible in all the patients in supine position and in sitting position before and after physical exercise without adverse effects. The clinical and baseline echocardiographic variables of both the patient groups are described in Table I. Compared to the 22 patients who were studied in the supine position, the 14 patients who were studied in the sitting position postexercise were tested soon after implant and were more likely to be females and to

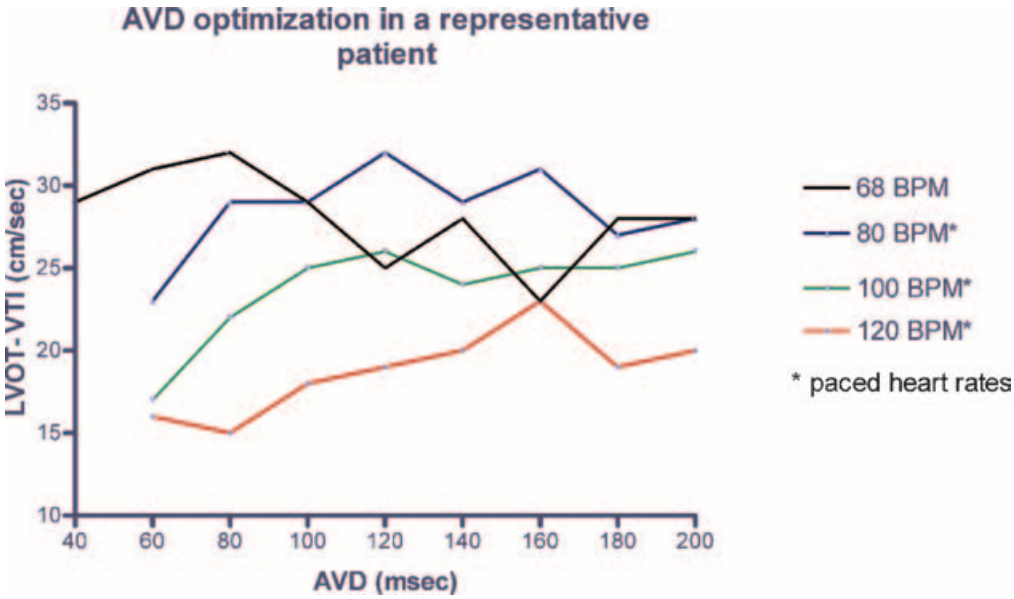

Figure 1. *AVD optimization at different paced hart rates (DDD Pacing) in a representative patient. Note the overall decrease in VTI as heart rates increase, but the relative benefit from AVD prolongation at increased heart rates.*

have nonischemic cardiomyopathy. The optimal AVD delay at rest was between 80 and 120 ms in 86% of the patients and tended to be longer in the supine than in the seated position.

The resting heart rate in the paced group showed a wide range from 50 to 100 bpm (mean 72 ± 13 bpm). During an increase in heart rate by DDD pacing, a gradual decline of VTI values was noted (Fig. 1). When 618 VTI values from AVD optimization at three different heart rates were analyzed in a repeated measures model, we found a linear relationship between the absolute heart rate and the effect of AVD on VTI: the VTI increased by a mean of 0.047 cm/s per 20 ms increase in AVD and 10 beats of heart rate ($P = 0.007$). The linear benefit of AVD prolongation persisted up to a heart rate of 110 bpm, after which the linear model was not accurate anymore. Because of the great variation of absolute VTI values in the heterogeneous patient group, the relative changes of VTI and AVD are depicted as percentage of baseline optimum (Fig. 2). In three patients with complete AV block, this effect tended to be more pronounced (VTI + 0.09 cm/20 ms AVD increase/10 bpm increase in heart rate, $P = 0.04$ vs VTI + 0.05 cm/20 ms AVD/10 bpm without AV block, $P = 0.02$, P interaction = 0.35).

In the second group of 14 patients, the sinus rate increased from a wide range of baseline rate 73.7 ± 13.4 (range 59–91 bpm) to 91.3 ± 13 bpm, (range 79–110 bpm). Variation of sinus rates during recovery was taken into account by analyzing the corresponding cycle length and a random order of AVD programming during recovery. As intrinsic conduction with loss of resynchronization was occurring at different AVD in each patient, only events during ventricular pacing were analyzed. Again, the analysis of 176 VTI measurements by a repeated measures model showed a similar and more pronounced linear benefit from AVD prolongation at increased heart rates. A 0.146 cm/s increase in VTI was noted per 20 ms prolongation in AVDs, per 10 bpm increase in heart rate, and $P = 0.013$ (Fig. 3). Intraindividual comparison of pre- and postexercise values showed a decrease of VTI by 0.44 cm/s per 20 ms AVD prolongation ($P < 0.0001$) preexercise, but an increase of VTI by 0.29 cm/sec per 20 ms AVD prolongation postexercise ($P < 0.001$; P interaction = 0.0001).

At maximum heart rates, the observed best AVDs were just 10–20 ms shorter than intrinsic conduction (Figs. 1 and 2). The beneficial effect of AVD prolonging was observed until a heart rate of 110/min was reached, after which these effects faded because of a rapid decline in cardiac function (Fig. 1).

No significant differences were found in patients tested immediately after implant ($n = 14$) and during follow up (268 ± 250 days postimplant, median 189, range 32–1214 days).

Discussion

During AV sequential pacing, the systolic performance of the failing ventricle is affected by the AV delay.[1,5] This study demonstrates that the relationship between AVD and left ventricular systolic

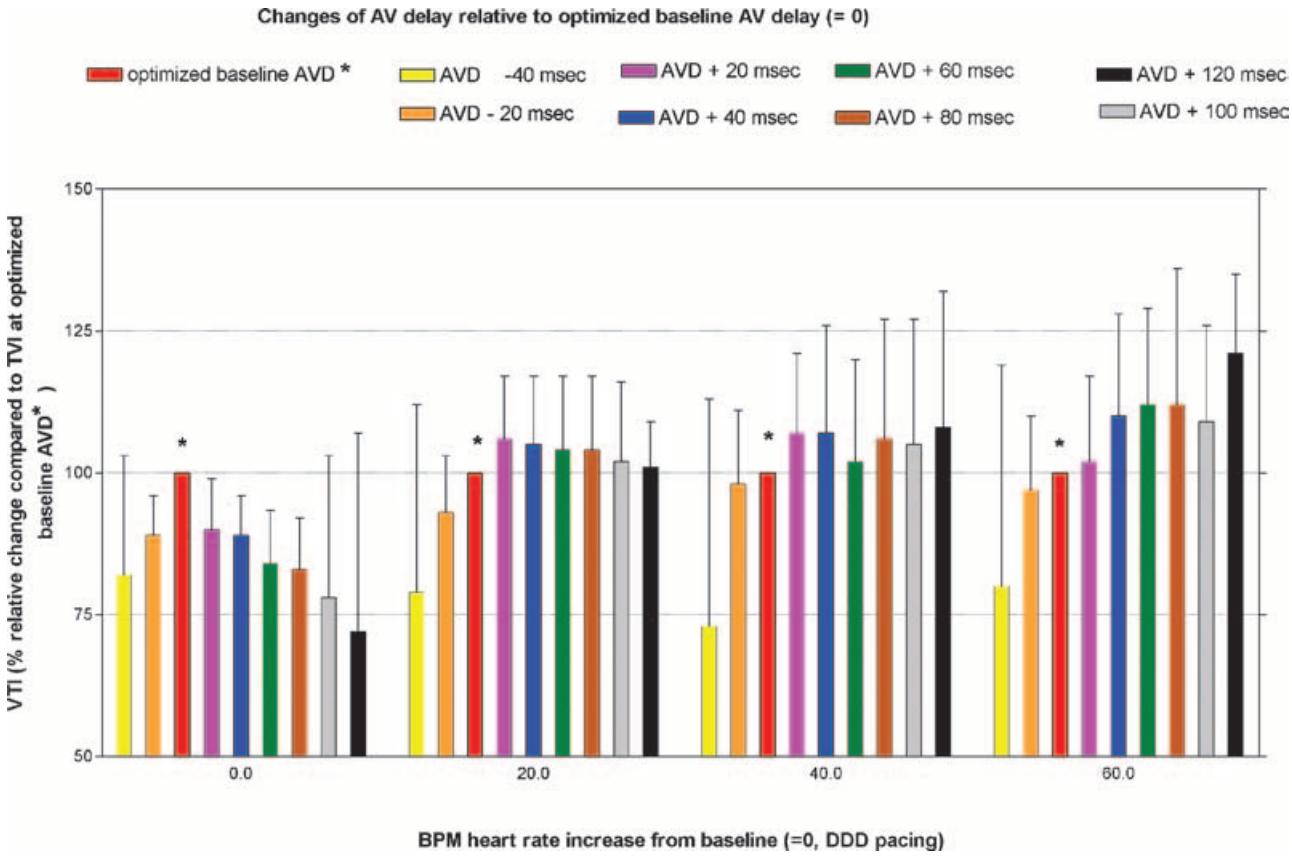

Figure 2. *Relative increases of VTI at different heart rates during AVD optimization. Note that VTI values are depicted as percentage of maximum of baseline optimization. Also AVD are depicted as relative increases from optimal baseline intervals.*

performance is not fixed and that the optimal AV delay varies with heart rate. CRT has been shown to improve mechanical performance of the left ventricle,[2,3] to reduce mitral regurgitation,[8,9] and improve exercise tolerance.[4,10] Optimal results from CRT in supine position and during physical exercise are dependent not only on effective mechanical resynchronization of ventricular contraction, but also on the atrioventricular interval.

Conventional dual chamber pacemakers use a dynamic rate adaptive shortening of AVD, which has been shown to improve exercise tolerance.[11] Similarly, in biventricular pacing devices, the AVD can be programmed either fixed delay or dynamic with a rate adaptive shortening. However, in previous multicenter CRT trials, a relatively short baseline AVD has been programmed around 100–120 ms in order to preexcite the left ventricle.[12,13] Therefore, the purpose of this study was to determine whether the dynamic AVD shortening is applicable in CRT or a fixed AVD would be preferable. To our own surprise, a lengthening of the AVD proved beneficial, when the heart rate was raised by pacing. Therefore, we studied a second patient group, where we eliminated the effects of atrial pacing on effective AVD by using a physiologic stress on increase *intrinsic* sinus rates. The same effect was observed and proved significant on intraindividual comparison using linear models for repeated measures as well over the entire group showing a direct linear benefit of an AVD prolongation depending on absolute heart rates. Of note, the AVD should be prolonged only as long as biventricular pacing is maintained. These observations were consistent in heterogeneous patients with respect to resting heart rates, EF, presence of AV block or mitral regurgitation, and in different settings, confirming the clinical relevance. The finding that forward flow in the LVOT is dependent on AVD at only a modest increase in heart rate, similar to the heart rates that occur during activities of daily living, underscores the clinical importance of our findings.

Our study does not provide data to elucidate the mechanism by which an increase in heart rate alters the optimal AVD. There are several possible explanations for the findings. Given the duration of the P wave being in the same range as optimized

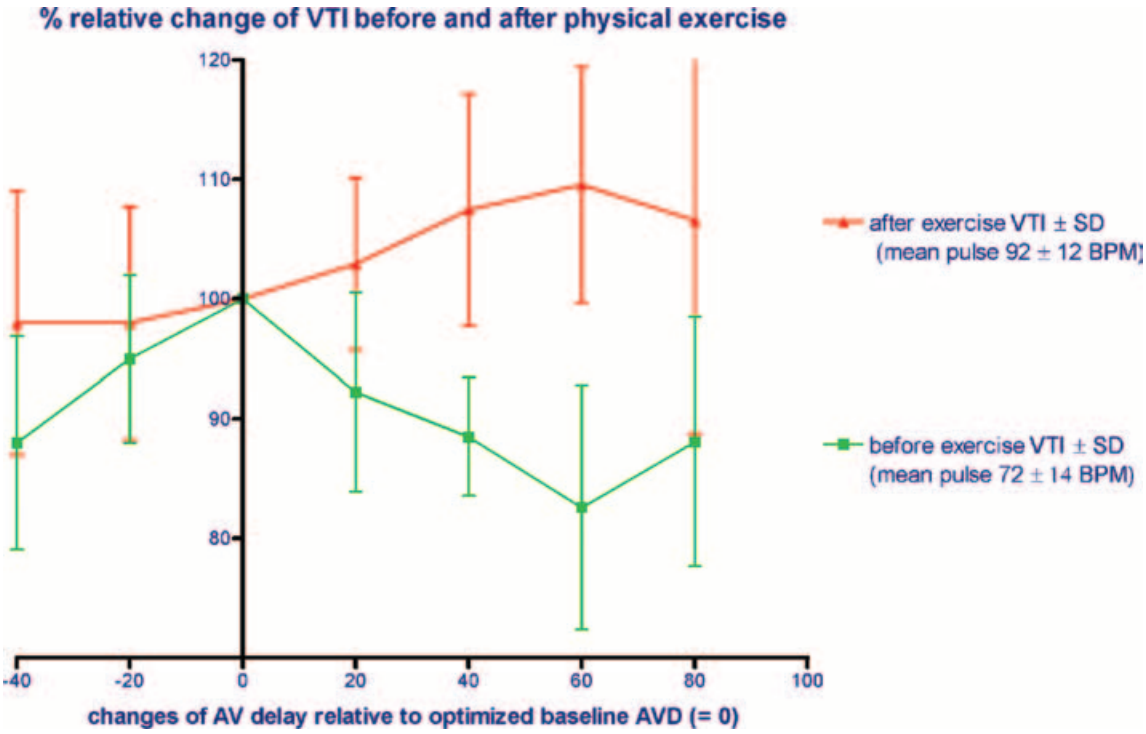

Figure 3. *Graphic demonstration of relative changes in VTI before (green) and after excercise (red). This two dimensional plot does not take heart rate into account, which changed for a mean of 20 bpm. AVD values are depicted as relative changes from optimal baseline interval.*

baseline AVD, the rate adaptive shortening of the latter might lead to simultaneous atrial and ventricular contraction. Second, progressive fusion at longer AVD might increase ventricular resynchronization during exercise. On the other hand, we observed a similar beneficial effect of AVD prolongation in paced patients with and without AV block. Third, the CRT patients with dilated ventricles require an elevated preload making them more dependent on an effective atrial systole. This dependence might become more obvious when ventricular filling times are shorter at increased heart rates. Most interesting was the finding that the beneficial effects of rate adaptive ADV prolongation were more prominent in the upright position (0.146 cm/s vs increase in VTI per 20 ms AVD prolongation per 10 bpm heart rate increase), than in the supine position (0.047 cm/s VTI increase). In previous studies, AVD optimization was performed in the supine position, and further studies are needed to determine the effect of body position on optimal AVD. Finally, the worsening of diastolic function during exercise might increase the relative importance of atrioventricular resynchronization over left ventricular resynchronization. Of note, the systolic function (LVOT-VTI) decreased at increased heart rates in many patients indicating a severe ventricular dysfunction. Therefore, the AVD optimization during exercise is more important in CRT than in normal pacemaker patients with preserved EF.

In previous multicenter trials, the AVD was programmed either fixed or with dynamic shortening.[2,10] The findings of our study might explain the substantial number of nonresponders during exercise tests in these studies. It is possible that the use of optimal AVD during exercise would increase the proportion of patients whose functional capacity is improved by CRT.

In conclusion, the systolic performance of the dilated ventricle, which depends on an elevated preload, is critically affected by the appropriate timing of the AVD during exercise. In contrast to normal pacemaker patients, in CRT, the relatively short baseline AVD should be prolonged at increased heart rates. Further studies with other means of measuring exercise cardiac performance are needed to confirm these unexpected findings.

Limitations

Different methods of AVD optimization exist and the reference has not been defined yet.[14] Because up to 10 different AVD had to be assessed before recovery of heart rate after physical exercise, we used LVOT-VTI as the only outcome parameter.

This may not reflect the impact of AV delay or CRT on other parameters of cardiac performance, such as mitral regurgitation and diastolic filling time. However, the VTI in the LVOT has been shown to correlate with other echocardiographic indices of cardiac performance during AVD optimization.[3] Further studies using other methods are needed to confirm these findings.

Another limitation is the wide range of resting heart rates and the fluctuation of postexercise heart rate during AVD optimization. In patients who had a rapid recovery of heart rate, a second exercise test had to be performed in order to measure all AVDs at increased heart rates. To overcome this issue, we included the cardiac cycle length as a continuous variable in the repeated measures model. The consistent findings in heterogeneous patients confirm the applicability of our results in unselected CRT patients.

Our study was not designed to address differences of body position on AVD optimization, which have not been addressed yet. The different findings in the two patient groups can therefore not be directly compared. On the other hand, the similar benefits of AVD prolongation in different settings strengthen our hypothesis irrespective of the body position.

Although the presence of AV block or significant mitral regurgitation, or the time interval after device implantation did not seem to significantly affect the findings of our study, the number of patients is too small for comparison of these subgroups in this pilot study.

Clinical Implications

Based on our findings, rate adaptive AVD programming in CRT should be different than in conventional pacemaker programming. Pacemakers that are commercially available may be programmed to have either a fixed or dynamic shortened AVD. The results of this study demonstrate that the dynamic AVD feature of pacemakers may be deleterious to left ventricular systolic function among patients with a dilated cardiomyopathy who are treated with CRT. Ideally, the AVD in these patients would increase with an increase in rate and not decrease. However, dynamic lengthening of the AVD is not an available feature in currently available pacemakers. The present study demonstrates the need for such a feature. Until dynamic lengthening of the AVD becomes available, clinicians should program fixed AVD.

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